Fazekas

September 11, 1957

Dear Stephen:

My apologies for the anguish you incurred; it could only be matched by the indecision of choosing the proper one of your prénoms.

Your remarks were most provocative— as I learn more and more, I may get the delusion of some understanding of the vexing issues. At this stage too, a single embarrassing fact should not be allowed to kill off an otherwise promising hypothesis. There would seem to be two aspects of I.V., between which one may not be able to build more than a tentative link —(1) the rationale of its generation, and (2) of its behavior. As for (2) I am happy to hear that the notion of a wall-defect is not altogether hors de combat. I have had some difficulty in broaching its plausibility to Burnet, partly because of my too evident disadvantage in appreciation of the background facts, but at the present time, I think it is possible to discuss it at least on the same plane as some more direct genomic damage. A lesion in the wall may be expected, in any case, to have some effect on the integrity of the genome.

In thinking further about the problem, I have been led to a somewhat different working hypothesis from F.&Graham '55, and would be delighted to hear your views on it. I realize there are details that should be patched up, but a number of ad hoc suppositions seem to be required for any of the current formulations.

a) Hypothesis: An infected cell yields I.V. when the cell surface is depleted of receptor substance at the time of emergence of the virus.

Thishypothesis has one plausible material formulation, that the cell surface in fact contributes to the virus skin. Different strains of virus may depend, to varying degrees on the completeness of this component of the cell surface.

Most of the data relied upon by F. & Graham are equally compatible with this version, as is theperiodate experiment itself. The differential prediction is that modification of the cell surface even after viral penetration would have the same effect. As far as I could determine, this was not reported.

On thishypothesis, I thought that RDE might furnish an even more specific way of altering the surface of infected cells than periodate. Of course the experiment proves to have been done, no less than by Cairns & Edney 1952! Looking further, I found the remark in v.Magnus' review (Adv V Res 2, 74) that "the discrepancies between.. embryonated eggs with..RDE-treated eggs" can be reconciled on the basis of a metabolic difference. To be sure: a) suggests a specific material interpretation. However, as far as I could quickly judge, there has been no attempt to verify the postulated RDE effect in a direct comparison. As onemeans of gaining some experience in the techniques here, I am planning to make that verification, though the experimental

result seems almost a foregone conclusion in view of what's already been published. Perhaps you already have the most relevant data yourself. There will still remain some questions of interpretation— if the experiment does work out, I will have to see what can be done by way of encouraging some chemical comparisons of complete and IV with regard to relative content of receptor polysaccharide.

Just one or two other points— the somewhat clumsy interpretation of single cycle virus of our previous discussion becames redundant; it becomes an attribute of the host cell under a). I am not quite sure, without the data, how to cope with single-cyclebehavior of other inactivated virus (UV, formalin?); this might be done as an aspect of multiplicity, viz. the concurrence of excess RDE-activity. Or not implausibly, the wall-building function of the genome might be more sensitive than the RNA replication, but I'm not too happy about this. The infectivity-potentiating effect of allantoic fluid might be the competitive protection of cell receptors.

Burnet's group is veering away from flu rather rapidly, and this sort of problem is rather marginal to their interests at the present time, though everyone has been as cordial and helpful as could be. I am really very sorry that I could not get the benefit of your own unique approaches at the same time, but the mail will have to do for the moment. Burnet rather discouraged me from trying to set up your shell-bit technique at present, thinking that as they've had no experience with it, it might take several weeks of my too limited time to work it up. Possibly there's some sense in this; I will certainly see that we do take advantage of it at Wisconsin. If there's any way to manage it, I'll try to stop over to Canberra; till then I hope we can keep in close touch this way.

Sincerely,

Joshua Lederberg